Clinical Case Report

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Multi-drug resistant *Enterococcus faecium* in late-onset keratitis after deep anterior lamellar keratoplasty

A case report and review of the literature

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Abstract

Rationale: Interface keratitis after lamellar keratoplasty is one of the causes of graft failure. We report the first case of microbiologically proven *Enterococcus faecium* infection following deep anterior lamellar keratoplasty (DALK) and review the available literature.

Patient concerns: A 37-years-old Caucasian man presented with pain, redness and severe vision loss in his right eye. Five weeks before, he underwent DALK using the FEMTO LDV Z8 in the same eye for the surgical correction of keratoconus.

Diagnoses: Upon presentation, slit-lamp biomiscroscopy revealed corneal graft edema with multiple infiltrates located in the graft-host interface.

Interventions: Therapeutic penetrating keratoplasty (PKP) was carried out in addition with cultures of the donor lenticule removal. Laboratory results isolated a multi-resistant *Enterococcus faecium* interface infection. According to the antibiogram, the patient was treated with systemic Tigecycline and Linezolid for 7 days.

Outcomes: During the following weeks, clinical features improved over time and no signs of active infection were visible seven months postoperatively.

Lessons: Early PKP showed to be a good therapeutic option with great anatomic and functional outcomes.

Abbreviations: BCVA = best-corrected visual acuity, DALK = deep anterior lamellar keratoplasty, MIC = minimum inhibitory concentration, OCT = optical coherence tomography, PKP = penetrating keratoplasty.

Keywords: deep anterior lamellar keratoplasty, *Enterococcus faecium*, interface infection, penetrating keratoplasty

1. Introduction

Deep anterior lamellar keratoplasty (DALK) represents an efficient technique for corneal diseases not affecting the endothelium. This technique presents many advantages over penetrating keratoplasty (PKP), such as the maintenance of globe integrity and the absence of irreversible graft rejection.[1] Interface keratitis after corneal transplantation is one of the causes of graft failure and is associated with poor vision. Although infrequent, keratitis after lamellar keratoplasty may threaten corneal graft clarity and may cause endophthalmitis with potential need for enucleation. Diagnosis and treatment of interface keratitis is a challenge, due to the deep stromal location that precludes access for microbial examination and topical drug penetration in the site of infection.[2] We describe herein the first case of *Enterococcus faecium* infection following DALK, successfully treated with targeted systemic therapy with Tigecycline and Linezolid associated with therapeutic PKP.

2. Case report

A 37-year-old Caucasian man was referred to our clinic for surgery evaluation in a case of advanced keratoconus in the right eye. His best-corrected visual acuity (BCVA) was 20/200 and preoperative topography (Sirius; Costruzione Strumenti Oftalmici, Florence, Italy) showed an Amsler–Krumeich stage IV keratoconus in the right eye (Fig. 1) and the patient was scheduled for a DALK.

On April 2018, the patient underwent femtosecond laser-assisted mushroom-configuration DALK in his right eye,

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Informed consent was obtained from the patient for publication of this case report and accompanying images.

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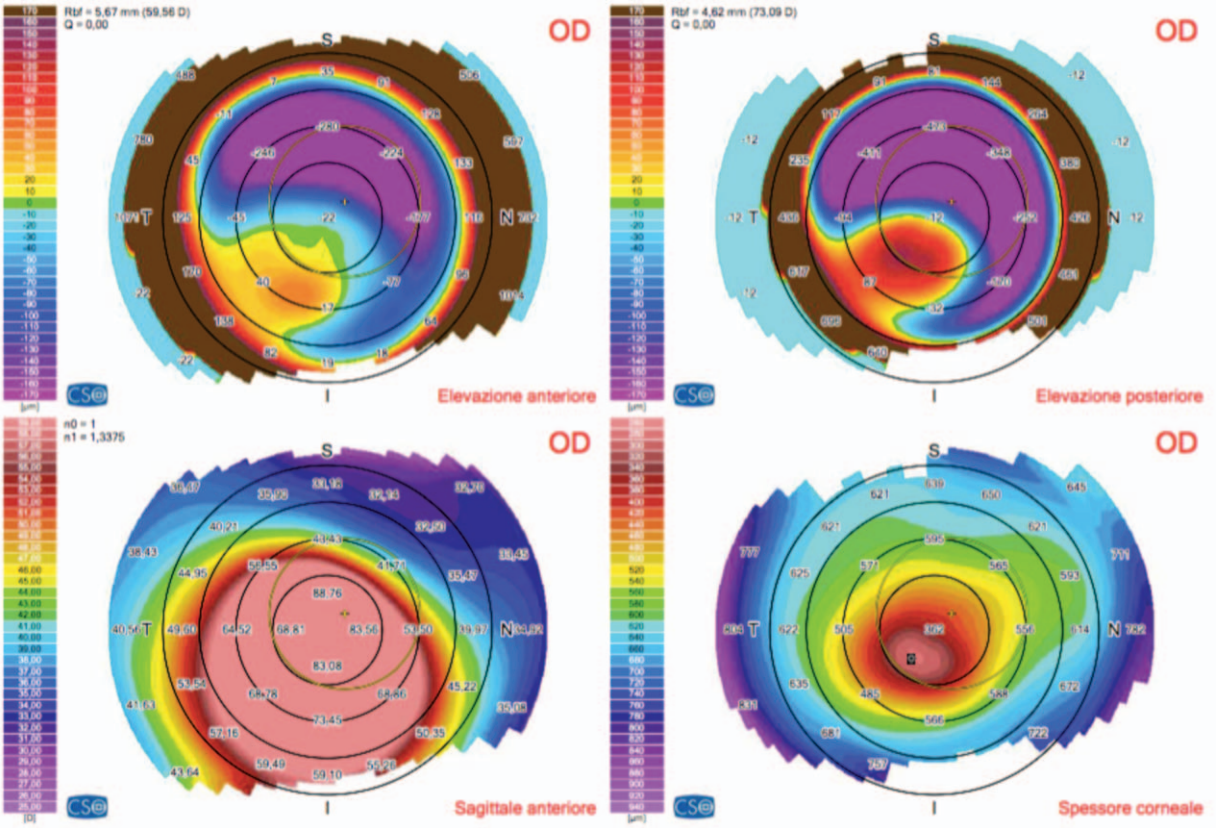

Figure 1. Topography showed an infero-temporal paracentral corneal steepening. Sim-K reading were 62.08 D and 72.68 D in the flat and steep axis respectively, with a corneal thinning point of 286 μm.

performed with the FEMTO LDV Z8 femtosecond laser (Ziemer Ophthalmic Systems AG, Port, Switzerland). Surgery was uneventful, and the early post-operative course was unremarkable. The patient was discharged 2 days after surgery, and was instructed to instill atropine 1% eye drops twice daily, chloramphenicol 0,5% and dexamethasone 0,1% eye drops 4 times daily associated with systemic ciprofloxacin 500 mg twice daily and prednisone 25 mg once a day. During the subsequent follow-up visits, no signs of active ocular infection were detected. Five weeks post-operatively, the patient presented at our Department with pain, red eye, and loss of vision in the operated eye. Visual acuity was limited to hand motion and slit-lamp examination revealed corneal graft edema with multiple whitish infiltrates (Fig. 2, part A); anterior segment-Optical Coherence Tomography (OCT) (MS-39) confirm the location of the infiltrates at the graft-host interface (Fig. 2, part B). Due to the suspicion of *Candida* infection, we started a topic and systemic therapy with Voriconazole. Since clinical picture continued to worsen despite therapy, therapeutic femtosecond laser-assisted PKP was performed to avoid endophthalmitis and to obtain a specimen for bacteriological examination. By using FEMTO LDV Z8, it has been possible to match the exact shape of the removed and donated tissue segments, so that the prepared donor transplant nestles perfectly in the opened eye. Aqueous cultures obtained before PKP were negative for bacterial and fungal growth. Excised cornea cultures yielded *E faecium*; it was tested for antibiotic susceptibility to 14 antibiotics and was found to be resistant to twelve antibiotics including: ampicillin, ampicillin/sulbactam, cefuroxime, clindamycin, erythromycin, gentamycin, imipenem, moxifloxacin, streptomycin, teicoplanin, tetracycline, and vancomycin. The antibiogram revealed that the microorganism was sensitive to tigecycline (minimum inhibitory concentration [MIC] ≤ 0.12) and linezolid (MIC = 2). Therefore, medical treatment was shifted to tigecycline 50 mg 2 times a day and linezolid 600 mg 2 times a day for a week as off-label regimen. Additionally, topical tetracycline 1% eye drop was prescribed every 4 hours. Clinical picture improved soon after targeted therapy and currently, at 7 month follow-up, the corneal graft is clear and BCVA is 20/25 (Fig. 2, part C).

3. Discussion

Enterococcus faecalis – formerly classified as part of the group D *Streptococcus* system – is a Gram-positive, commensal bacterium habiting the gastrointestinal tracts of humans and other mammals.[4] They are a leading cause of nosocomial infection, resistant to many antimicrobials, especially vancomycin-resistant.[5] Although *Enterococci* have been described as a relatively uncommon cause of endophthalmitis post-keratoplasty,[6] to the best of Authors' knowledge *E faecium* graft infection following DALK has not yet been described.

We performed an extensive review of the literature about ocular infection after DALK using the Medline/Pubmed database

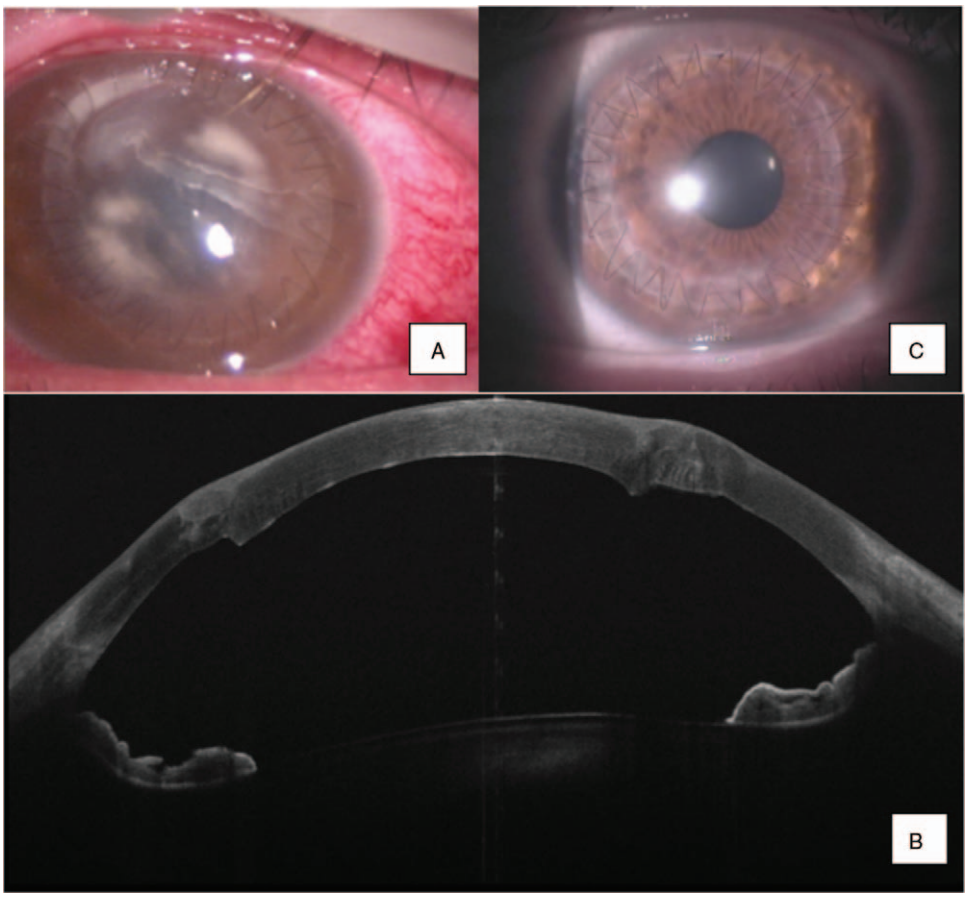

Figure 2. (A) Multiple whitish infiltrates with less defined margins are visible at the donor–recipient interface 5 weeks after surgery (B) Anterior segment-OCT shows infiltrates at the graft-host interface (C) Clear graft 7 months after therapeutic penetrating keratoplasty.

from January 2000 to February 2019. The free-text search terms "keratitis", "interface", "infection", "keratoplasty," and "lamellar" were used. Two independent observers (F.D. and A.G) reviewed the abstracts to determine the eligibility of studies for inclusion. Articles that presented aggregate patient data (e.g., clinical trials in which data on individual patients were not reported) were excluded. A total of 84 relevant publications were identified. Of these studies, specific case information was available for 17 cases.[3,7–21] The salient clinical findings of these cases are summarized in Table 1.

According to the literature, the development of multiple infiltrates located in the donor-recipient interface was the first sign of keratitis, without any signs of inflammation in the anterior chamber. Laboratory investigations, including either corneal scraping or excised cornea culture, were taken to identify the microorganism and yielded *Candida* spp.,[3,7,9,12,14,16,21] *Klebsiella pneumonia*,[8,17] *Alternaria*,[10] *Mycobacterium chelonae*,[11] *Aspergillus flavus*,[13] Gram-positive *Cocci*,[15] *Actynomices*,[18] *Lecytophora mutabilis*[19] and *Herpes simplex virus*.[20] Infectious pathogens were identified from cultures of the excised donor buttons in almost all cases and from the culture and smear tests from the material employed to irrigate the graft–host interface in 1 case. Donor rim cultures resulted positive in 3 of 5 cases, with correspondence to the organisms identified in the recipients. In our case, microbiological analysis of the excised donor button disclosed the diagnosis of *E faecium* infection.

None of these patients developed endophthalmitis: these data suggest that in anterior lamellar keratoplasties, the Descemet Membrane in capable to avoid or at least delay the intraocular penetration of microorganism. Although the development of endophthalmitis may be hampered in the setting of postoperative DALK interface infection, the typical location at the interface could be more difficult to treat, making conventional approach to the treatment of microbial keratitis more likely to fail. In fact, none except 1 case responded to medical treatment alone[7] and almost all the reported cases of infection required subsequent surgical treatment, either donor button exchange or PKP, to resolve the infection.

The result of our case should be interpreted in the light of certain limitations. Specifically, donor rim cultures were not performed, and the possibility of donor contamination cannot be ruled out.

Our report provides evidence of the protective property of DALK of hampering the direct intraocular penetration of microorganisms in case of donor graft microbial contamination, allowing good outcome, obtain with PKP, even in case of multi-resistant bacterium.

Table 1

Included studies in chronological order and main clinical patient characteristics.

Author, Year [reference]	# of cases (age, gender)	Primary pathology	Infection onset	Clinical presentation	Laboratory diagnosis	Pathogen	Management	BCVA (Snellen)
Kodavoor SK et al (2016)[7]	One (32, F)	keratoconus	89 days	Dense infiltrates, streak hypopyon	Corneal scraping	*Candida albicans*	Medical therapy	20/80
Bajracharya et al (2015)[8]	One (42, F)	Granular dystrophy	1 day	Interface infiltrates with severe anterior chamber reaction	Excised donor cornea culture	*Klebsiella pneumoniae*	Donor button exchange + PKP	nr
Le et al (2015)[9]	One (31, M)	keratoconus	4 days	Interface deposits	Corneal scraping and excised cornea culture	*Candida glabrata*	Donor button exchange + PKP	20/40
Naik et al (2014)[10]	One (30, M)	Corneal leucoma	3 months	Large brown pigmented dry lesion	Corneal scraping	*Alternaria*	Donor button exchange	20/60
Murthy et al (2013)[11]	One (26, F)	keratoconus	3 months	Multiple round opacities at the interface	Corneal scraping	*Mycobacterium chelonae*	Donor button exchange + PKP	20/40
Wessel et al (2013)[12]	One (39, M)	keratoconus	5 days	Whitish round retro-corneal infiltrates	Excised corneal culture	*Candida orthopsilosis*	PKP	20/630
Jafarinasab et al (2012)[13]	One (28, F)	keratoconus	4 days	Interface infiltrates	Excised corneal culture	*Aspergillus flavus*	Donor button exchange	20/60
Sedaghat et al [14]	One (18, F)	keratoconus	4 months	Keratic precipitates	Irrigating cultures	*Candida albicans*	Medical therapy	20/30
Lyall et al (2012)[15]	One (44, M)	Lattice corneal dystrophy	4 months	Stromal infiltrate	Excised corneal culture	Gram-positive *Cocci*	DALK	20/40
Bahadir et al (2012)[16]	One (23, F)	keratoconus	4 weeks	White cream color deposits	Corneal scraping	*Candida* spp.	PKP	nr
Zarei-Ghanavati et al (2011)[17]	One (35, F)	keratoconus	2 days	Multiple white deposits confluent	Excised corneal culture	*Klebsiella pneumoniae*	PKP	20/20
Caretti et al (2011)[18]	One (21, M)	keratoconus	6 days	Multiple whitish patches	Excised corneal culture	*Actynomices*	PKP	20/25
Fintelmann et al (2011)[19]	One (53, F)	Corneal ulcer	One week	endophthalmitis	Excised corneal culture	*Lecytophora mutabilis*	PKP	nr
Eberwein et al (2008)[20]	One (45)	Keratoconus and severe atopic disease	*Available only in German text*	Corneal melting	*Available only in German text*	*Herpes simplex virus*	PKP	*Available only in German text*
Kanavi et al (2007)[21]	Two (21, M)	keratoconus	2 months	Cream color deposits interface	Irrigation fluid and corneal button	*Candida glabrata*	PKP	nr
	(25, M)	keratoconus	2.5 months	Interface infiltration and vascularization	Corneal culture	*Candida albicans*	PKP	nr
Fontana et al (2007)[3]	One (30, M)	keratoconus	4 weeks	Multiple interface infiltrates	Donor rim culture	*Candida albicans*	Donor button exchange + PKP	20/25

BCVA = best-corrected visual acuity, DALK = deep anterior lamellar keratoplasty, F = female, M = male, nr = not reported, PKP = penetrating keratoplasty.

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